**Waking Up Anna**

By Kate O’Toole1, and Shuchismita Dutta2\*

1Department of Biology, Emory University, Atlanta, GA 30322

2Institute of Quantitative Biomedicine, Rutgers University, Piscataway NJ 08854

\*contact author: sdutta@rcsb.rutgers.edu

**Part 5. When you Take a Sedative …**

The natural ligand GABA binds to the GABA-A receptor to produce an inhibitory effect by opening chloride channels. What do you think happens to these receptors when individuals who are unable to sleep, take a sedative like valium (a benzodiazepine)? In this section we will explore what happens to the GABA-A receptor when you take valium.

Open another structure in RCSB – GABA-A receptor in complex with GABA and Valium (PDB ID 6hup). Valium is an example of a benzodiazepine.

Scroll down in the Structure Summary to find Small Molecules

Q1 (3 pts). Complete the table below:

:

|  |  |  |  |
| --- | --- | --- | --- |
| **Small molecule abbreviation** | **Chains that it interacts with** | **Complete chemical name** | **Identify which complete chemical name indicates GABA and which is Valium** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Q2 (1 pt). Click on the Small molecule abbreviation for Valium and include the chemical structure below.

Return to the Structure Summary page for 6hup.

* To the right of the Valium entry in the Small Molecules section, click on the Ligand Interaction button on the right hand side. This will go to the 3D view (Mol\*) focusing in on the ligand (valium) interacting with the protein structure.
* Using the Sequence window, pull down the Name of the Valium molecule in the list. *The abbreviation should show up where sequence information was before.*
* Present the Valium
  + In a space filling model – Select Valium representation > Ligand > … > Add representation > Spacefill
  + Color the Valium orange (Select > Paintbrush > Orange)
  + Label the Valium (Select > Measurements > Add > Label)
    - *This should be labeled as DZP502*
  + Label the amino acids that form chemical bonds with Valium at this location (there are 3 locations in the model).

Q3 (2 pts) What are the two amino acids, positions (numbers) and chains that react with this Valium? Include an image of your labeled structure.

Where do the Valium molecules bind relative to the GABA molecule?

* Click on the toolbar icon Reset icon (looks like a recycle sign). This should zoom outward from your model.
* Click on Entity > subunit > paintbrush > gray.
  + Repeat for all 3 polypeptide subunits (alpha, beta and gamma)
* Identify the GABA molecules based on where you observed them in Part 4.
  + Click on Chain > click on GABA and color each yellow
* There are three Valium molecules shown bound to this model. Two are indicated/labeled as 502 and you just identified the binding sites for one of them in Question 3.
  + Click on the two 502 molecules (located in a similar region of the structure) and color each orange.
  + Identify the third Valium in the structure (binds in a different location and may not be functional). Color that Valium purple.

Q4 (2 pts). Where in the structure are the GABA and Valium molecules bound? Which GABA-A receptor chains are they bound to? Support your answer with a figure.

*Box 2: Vocab (previously seen in Part 1)*

**Agonists**: These are drugs or molecules that turn on the function of a protein. The natural ligand usually acts as an agonist.

**Antagonists**: These are drugs or molecules that decrease or inhibit the function of a protein.

**Allosteric modulators**: The word root “allo” means “other”. These are drugs or molecules that bind at a location other than the natural ligand’s binding site. Modulators could be positive (increase activity of the protein) or negative (decrease its activity).

Q5 (1 pts). Based on the location of valium bound in this structure what can you say about the nature of GABA and valium interaction (use the information in Box 2 to help with your description?